REMARKS

I. The new claims and amended claims are supported by the specification.

The claims are directed to full length polypeptides, 95% variant polypeptides, and fragments thereof, the polynucleotides encoding such polypeptides, and hybridizing variant polynucleotides. In addition, the claims are directed to methods of screening for modulators of aspartyl protease activity using these polynucleotides and polypeptides. The recited aspartyl protease activity involved in APP processing is characterized in the art and is summarized in the specification at page 2, lines 20-24. The claimed subject matter is supported throughout the specification and does not add new matter to the application.

Claims 151, 155 and 156 recite polypeptides that lack "a transmembrane domain." The specification teaches that the transmembrane domain spans residues 455-472. (See page 21, lines 5-6). Soluble fragments such as those which lack a transmembrane domain are contemplated at page 17, lines 18-22, page 31, lines 14-16, and page 38, lines 4-6.

Claims 151, 153, 155, 158, 171, 173, 175, and 176 recite polypeptide fragments that include "aspartyl protease active site tripeptides DTG and DSG." Active fragments of SEQ ID NO: 4, where the activity is processing APP into amyloid beta, are supported at page 28, lines 27-29 and page 31, lines 3-6. The application teaches that the tripeptides DTG and DSG found in the Asp2 amino acid sequence are important active site motifs, and the claim uses these tripeptides to further define the claimed polypeptides. The aspartyl protease active site is generally described in the specification as being "embedded in the short tripeptide motif DTG, or more rarely, DSG." (See page 26, lines 10-11). Since DTG occurs at positions 93-95 and DSG occurs at positions 289-291, fragments that include these tripeptides include residues 93-291 and comprise the catalytic domain necessary for exhibiting aspartyl protease activity. The specification particularly contemplates fragments of SEQ ID NO: 4 comprising the DTG and DSG tripeptide active site amino acids by stating "Fragments of Hu-Asp within the scope of invention include those that contain the active site domain amino acid sequence DSG, fragments containing both the DTG and DSG active site sequences." (See page 31, lines 9-11). The active site tripeptides DTG and DSG each occur only once in SEQ ID NO: 4.

Claims 151 and 155 are directed to polypeptides that are 95% identical to a fragment of SEQ ID NO: 4 that retains aspartyl protease activity involved in processing APP into amyloid beta and lacks a transmembrane domain. The specification as a whole contemplates and teaches modifications of the polypeptides of the inventions, such as deletions, insertions, and substitutions, to produce amino acids sequences that differ from, but are at least 95% identical to, the human Asp2 sequences taught in the application. (See, *e.g.*, p. 33, lines 10-17. See also p. 5, lines 7-8; p. 8, lines 7-9; and p. 9 lines 9-11) Also contemplated and described were modifications to remove a transmembrane domain and thereby make the Asp2 soluble, all while retaining a useful biological activity of the Asp2 polypeptides, namely, the proteolytic activity involved in processing APP into amyloid beta. The DTG/DSG motifs and transmembrane-deleted fragments are described together in the paragraph bridging pages 30-31. The DTG/DSG motifs and 95% sequence variation are described together throughout the summary of invention, including at pages 5 and 8.

Claims 156, 171, 175, 189, and 195 recite "stringent hybridization conditions." These hybridization conditions are supported in the specification at page 10, lines 4-7. Claims 151 and 152 recite "heterologous peptide tags." These heterologous tags are supported in the specification at page 37, lines 16-20. Claims 154, 155, and 167-169 are directed to mammalian, human and insect host cell lines. These host cell lines are supported in the specification at page 11, lines 15-18. Claim 189 recites "conservative substitute" amino acid, which is supported at page 31, lines 3-12. Claims 165, 166 and 169 recite a "heterologous control sequence", which is supported at page 36, lines 13-18.

The specification also supports the genus of *biologically active* fragments that was claimed. Fragments which lack a transmembrane domain were contemplated and described for use in assays to identify modulators of aspartyl protease activity, such as β-secretase activity at page 17, lines 18-22. Methods of preparing soluble fragments, such as those without a transmembrane domain, were contemplated and described at page 19, lines 20-24. Deletion of the transmembrane domain to prepare soluble forms of Asp2 were contemplated at page 31, lines 14-16. Specific transmembrane-deleted fragments are discussed at pages 31-33. The Applicants provide a working example demonstrating preparation of a fragment of Asp2 in Example 10 (see pages 75-78). In that example, elution of the transmembrane-deleted, tagged Asp2 product was monitored in part by a beta secretase

activity assay (see p. 76, lines 25-26) taught in Example 12. Thus, the applicants have shown that the transmembrane-deleted form of this enzyme retains biological activity involved in APP processing. The demonstration of biological activity for the transmembrane deleted fragment, and the teaching of appropriate activity assays (including a variety of APP substrates), shows that the present claims are commensurate in scope with the teachings in the application. Using the teachings in the application, routine screening is all that is required to test the genus of variants encompassed by the structural limitations of the claims for the biological activity recited in the claim.

II. The new and amended claims are supported by the priority application.

The claims also find support in priority application no. 60/101,594 (hereinafter '594) filed September 23, 1998. The 1998 priority application explicitly contemplates Asp2 polypeptide fragments that exhibit aspartyl protease activity. (See page 3, lines 30-32 of '594) The 1998 priority application teaches that aspartyl protease activity involves processing APP into amyloid beta. (See page 2, lines 4-5; page 13, lines 12-13 and page 23, lines 9-12 of '594) The application also provides a working example demonstrating that Hu-Asp2 is involved in processing APP into amyloid beta (See Example 7 at pages 29-30 of '594).

The 1998 priority application teaches the structural characteristics necessary for the fragment to retain aspartyl protease activity. In particular, the specification teaches that "aspartyl proteases...possess a two domain structure which folds to bring two aspartyl residues into proximity within the active site. These are embedded in the short tripeptide motif DTG, or more rarely, DSG." (Page 5, line 2-6 of '594) The 1998 priority application also teaches that the predicted amino acid sequence of Hu-Asp2 "preserves the aspartyl protease active site triad" (see page 19, lines 25-26 of '594) and contains a "duplicative aspartyl protease site motif DTG/DSG separated by 194 amino acid residues." (See page 19, lines 11-13 of '594).

Polynucleotides which encode variants polypeptides with 95% identity to native Hu-Asp2 sequences, such as SEQ ID NO: 4, are supported at page 7, lines 10-12 of '594. The recited hybridization conditions are described at page 8, lines 14-16 of '594. Vectors comprising the Asp2 polynucleotides are supported at page 4, lines 11-14 of '594. A signal sequence is supported at page 10, lines 1-9 of '594. Host cells are supported at page

11, lines 8-11 of '594. Conservative substitutions are supported at page 7, lines 29-33. Heterologous expression control sequences are supported at page 9, lines 11-22.

III. Documents cited in the IDS submitted herewith.

An IDS and PTO/SB/08A which lists several documents was submitted on May 27, 2003. The Applicants believe the claimed polynucleotides and polypeptides are neither disclosed nor suggested by the prior art documents listed in the PTO/SB/08A.

A. Powell *et al.*, EP0855444 and U.S. 6,319,689 (B7 and A41 on IDS)

Powell *et al.* EPO855444 ('444) and U.S. 6,319,689 (hereinafter Powell '444) disclosed a polypeptide with 99.6% similarity to SEQ ID NO: 4. Some of the claimed polypeptides lack a transmembrane domain and can exhibit aspartyl protease activity involved in APP processing. The present application explains that the full length Asp2 protein has a transmembrane domain near its C-terminus. This discovery would not have been expected from other aspartyl proteases that had been described in the art, such as renin, pepsinogen, pepsin, and cathepsin D.

Powell '444 purports to disclose a deduced amino acid sequence of a protein called Asp2, but Powell '444 fails to teach or suggest that Powell's Asp2 has a transmembrane domain at all, and certainly does not teach to remove a transmembrane domain for any reason. Likewise, Powell '444 does not by chance teach any specific Asp2 fragment that lacks the region identified by the Applicants as a transmembrane domain of Asp2 in the present application.

In addition, some of the claimed polypeptides comprise the full length sequence of SEQ ID NO: 4. The polypeptide disclosed in Powell '444 is not 100% identical over the full length of SEQ ID NO: 4. Therefore, Powell '44 does not teach or suggest the full length polypeptide sequence of SEQ ID NO: 4.

For these reasons, the protein disclosed in Powell '444 is not within the scope of the amended claims.

B. Powell *et al.* EP 0848062 and US 6,025,180 (B5 and A10 in IDS)

In Powell *et al.*, EP 0848062 and US 6,025,180 (hereinafter Powell '062). disclose a polypeptide with 71% similarity and 46% identity to SEQ ID NO: 4. As explained

above in the context of Powell '444, a disclosure of a full length protein is not a disclosure of particular fragments that could be said to anticipate any claim. Moreover, the claimed polypeptide fragments are limited to those which comprise an amino acid sequence which is at least 95% identical to an active portion of the amino acid sequence of SEQ ID NO: 4. For this reason, too, the protein disclosed in Powell '062 is not within the scope of the amended claims.

C. Chrysler et al., WO 96/40885 (B2 in the IDS)

Chrysler *et al.* WO 96/40885 teaches a protein isolated from human 293 cells that exhibits β-secretase activity. The amino acid sequence of the protein is not disclosed by Chrysler *et al.* Although the amino acid sequence of Chrysler is admitted to be undisclosed, and the protein cannot be considered to inherently comprise a mammalian Asp2 peptide which exhibits aspartyl protease activity involved in processing APP into amyloid beta and lack a transmembrane domain.

The law says that mere possibilities are not sufficient to support an anticipation rejection premised on inherency. See, e.g., *In Re Oelrich* 666 F2d 578, 581 (Fed. Circ. 1981). The numerous proteins cited in the Evin *et al.*, reference (C2 in IDS) show that the presence of β-secretase-like activity in prior art polypeptides was insufficient to conclude that a protein preparation comprises the biologically relevant β-secretase, or the Asp2 of the claimed invention, as opposed to other proteins.

Moreover, Chrysler's protein preparation was from cells that are "naturally" expressing the protein(s) in the preparation. Even if Chrysler's protein preparation contains Asp2, the only reasonable conclusion to be drawn would be that it contains the Asp2 encoded by the Asp2 gene, which, as taught in the present application, naturally contains a transmembrane domain and cytoplasmic domain. (The present application also teaches recombinant methods for deleting the transmembrane domain, *e.g.*, expressing an Asp2 fragment lacking the transmembrane domain). Since some of the claimed polypeptides lack a transmembrane domain, they are neither disclosed nor suggested by Chrysler. For these reasons, the protein disclosed in Chrysler *et al.* is not within the scope of the amended claims.

IV. Declaration of Dr. Bienkowski under 37 CFR §1.132

In reviewing the earliest priority document (60/155,193), the Applicants have determined that the location of the transmembrane domain within Asp2 as recited in the priority document was misstated due, apparently, to an oversight during preparation of the application. The priority document describes the transmembrane domain as spanning approximately residues 392 to 417 (See page 20 lines 8-10 of 60/155,493) of the longer Asp2 splice variant. This description represents a shift of approximately 63 residues toward the carboxy-terminus, as compared to location of the transmembrane domain described in the present application (approximately residues 455 to 477). (See page 21, lines 4-5, of the Specification). As explained in detail in the Declaration of Michael Bienkowski filed herewith, the error occurred because the transmembrane domain was identified by scientists that were analyzing a partial Asp2 sequence that lacked about 63 amino-terminal residues of the complete Asp2 sequence. The scientists correctly identified the transmembrane domain residues, and also correctly assembled a full-length cDNA sequence. The priority application presented the full length sequence, but inadvertently used the numbering scheme of the partial clone to identify the location of the transmembrane domain.

To expedite prosecution and help eliminate prior art issues that might arise under §102(e)-(g), the Applicants have filed a declaration herewith which explains the circumstances described above in greater detail, and demonstrates that the Applicants had achieved the following prior to the filing date of the priority application (September 24, 1998):

(1) identified and characterized the full length Asp2 cDNA and deduced amino acid sequence;

(2) identified the location of a transmembrane domain in the Asp2 sequence (which corresponds with the transmembrane domain taught in the present application); and

(3) constructed an expression vector comprising an Asp2 cDNA sequence in which the codons encoding the transmembrane domain had been removed to provide a cDNA and vector encoding a transmembrane-deleted Asp2 fragment.

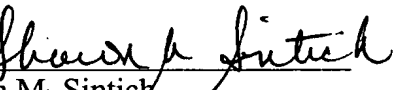
The declaration also explains that the Applicants worked diligently to express an active, transmembrane-deletion Asp2 polypeptide using different prokaryotic and eukaryotic expression systems. This declaration should serve to antedate any "intervening" prior art under §102(e)-(g) that the Examiner might identify for the period between their earliest priority date in 1998 and their next filing date in 1999, when the location of transmembrane domain is correctly taught. All dates have been redacted in the exhibits attached to the declaration.

CONCLUSION

In light of the forgoing amendment and remarks, the Applicants believe new claims 151-198 are in condition for allowance and early notice thereof is earnestly solicited.

Dated: June 19, 2003

Respectfully submitted,

By 

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